PCT/EP2004/010701

17.11.2004

PA 1235876

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APPLICATION NUMBER: *60/505,255*
FILING DATE: *September 23, 2003*

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

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M. K. HAWKINS
Certifying Officer

Docket Number	4-33382P1

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EL 997255120 US	September 23, 2003
Express Mail Label Number	Date of Deposit

Address to: **MS: Provisional Patent Application**
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PATENT COVER SHEET FOR PROVISIONAL APPLICATION

Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

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TITLE OF THE INVENTION (280 characters max)

COMBINATIONS OF THERAPEUTIC AGENTS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

- ☒ Specification (including Any Claims and Abstract) - 40 pages
- ☐ Drawings - sheets
- ☐ Other (specify):

METHOD OF PAYMENT

The Commissioner is hereby authorized to charge filing fee and any additional fees required to Deposit Account Number: 19-0134 in the name of Novartis.	PROVISIONAL FILING FEE AMOUNT: $ 160

☐ U.S. Government agency and contract number: (if the invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.)

Respectfully submitted,

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Date: September 23, 2003

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COMBINATIONS OF THERAPEUTIC AGENTS

The invention relates to a method of preventing or treating diseases characterized by cell proliferation and inflammation, coronary disease, hypertension, renal diseases, diabetes, and ocular diseases and conditions in a mammal, particularly a human, with a combination of pharmaceutical agents which comprises:

(a) a Vascular Endothelial Growth Factor (VEGF) receptor protein tyrosine kinase inhibitor (VEGF inhibitor); and

(b) one or more second therapeutic agents.

The invention further relates to pharmaceutical compositions comprising:

(a) an VEGF inhibitor;

(b) a second therapeutic agent; and

(c) a pharmaceutically acceptable carrier.

The present invention further relates to a commercial package or product comprising:

(a) a pharmaceutical formulation of an VEGF inhibitor; and

(b) a pharmaceutical formulation of a second therapeutic agent for simultaneous, concurrent, separate or sequential use.

The combination partners (a) and (b) can be administered together, one after the other or separately in one combined unit dosage form or in two separate unit dosage forms. The unit dosage form may also be a fixed combination.

Background of the Invention

In the center of the network regulating the growth and differentiation of the vascular system and its components, both during embryonic development and normal growth and in a wide number of pathological anomalies and diseases, lies the angiogenic factor known as VEGF or VGEF; originally termed Vascular Permeability Factor (VPF), along with its cellular receptors. See Breier et al., *Trends Cell Biol*, Vol. 6, pp. 454-456 (1996) and references cited therein.

VEGF is a dimeric, disulfide-linked 46-kDa glycoprotein produced by normal cell lines and tumor cell lines. It is an endothelial cell-specific mitogen, shows angiogenic activity in *in vivo* test systems, e.g., rabbit cornea, is chemotactic for endothelial cells and monocytes, and induces plasminogen activators in endothelial cells, which are then involved in the proteolytic degradation of extracellular matrix during the formation of capillaries. A number of isoforms of VEGF are known, which show comparable biological activity, but differ in the type of cells that secrete them and in their heparin-binding capacity. In addition, there are other members of the VEGF family, such as placenta growth factor and VEGF-C.

VEGF receptors are transmembranous receptor tyrosine kinases. They are characterized by an extracellular domain with seven immunoglobulin-like domains and an intracellular tyrosine kinase domain. Various types of VEGF receptor are known, e.g., VEGFR-1, VEGFR-2 and VEGFR-3.

Accruing evidence suggests that VEGF inhibitor are even more efficacious when used in combination with other therapeutic agents. There are both synergistic and additive advantages, both for efficacy and safety. Therapeutic effects of combinations of therapeutic agents with VEGF inhibitor can result in lower safe dosages ranges of each component in the combination.

Summary of the Invention

The invention relates to a method of preventing or treating diseases triggered by diseases characterized by cell proliferation and inflammation, coronary disease, hypertension, renal diseases, diabetes and ocular diseases and conditions in a mammal, particularly a human, with a combination of pharmaceutical agents which comprises:

(a) a VEGF receptor protein tyrosine kinase inhibitor (VEGF inhibitor); and

(b) one or more second therapeutic agents.

The invention further relates to pharmaceutical compositions comprising:

(a) an VEGF inhibitor;

(b) one or more second therapeutic agents; and

(c) a pharmaceutically acceptable carrier.

The present invention further relates to a commercial package or product comprising:

(a) a pharmaceutical formulation of an VEGF inhibitor; and

(b) a pharmaceutical formulation of a second therapeutic agent for simultaneous, concurrent, separate or sequential use.

The Therapeutic Agents

The term "second therapeutic agent" is a broad one covering many therapeutic agents having different mechanisms of action.

By the term "therapeutic agent" is meant especially any therapeutic agent other than a VEGF inhibitor or a derivative thereof. It includes, but is not limited to,

i. angiostatic steroids;
ii. photodynamic therapy;
iii. implants containing corticosteroids;
iv. AT1 receptor antagonists;
vi. ACE inhibitors;
vii. cyclooxygenase inhibitors;
viii. IGR-1R inhibitors;
ix. mTOR kinase inhibitors;
x. somatostatin receptor antagonists;
xi. PI3K inhibitors;
xii. Raf kinase inhibitors; and
xiii. PKC inhibitors.

Angiostatic steroids as used herein refers to agents which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone, hydrocortisone, 11-α-epihydrocotisol, cortexolone, 17α-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

Photodynamic therapy (PDT) as used herein refers to the use of a photosensitize agent activated by a laser. A preferred PDT treatment having a photosensitize agent and laser treatment protocol is disclosed in the issued European Patent 680 365 B1 and in the International Application WO 97/33619. In PDT, the photosensitive agent accumulates in the ocular tissue affected by CNV, i.e., the target ocular tissue, and is activated by a laser having a wavelength absorbable by the photosensitive agent. In the present invention, the

VEGF-inhibitor is administered before, after and/or simultaneously with the photosensitizer used in the PDT treatment. The combination of PDT with a VEGF-inhibitor may also referred to as adjunctive PDT.

The VEGF-inhibitor may be administered either sequentially or simultaneously with the photosensitive agent, the preferred method being the simultaneous, being a fixed combination.

The preferred photosensitizers are selected from the group of a chlorine, a bacteriochlorine, a phthalocyanine, a porphyrin, a purpurin, a merocyanine, a pheophorbide and a psoralen.

A highly-preferred photosensitizer is selected from the porphyrins and is typically the so-called green porphyrin or BPD-MA., which is marketed under the tradename Visudyne®.

Any of the photosensitive compounds described above can be used in the method of the invention. Of course, mixtures of two or more photosensitive compounds can also be used; however, the effectiveness of the treatment depends on the absorption of light by the photosensitive compound so that if mixtures are used, components with similar absorption maxima are preferred.

Implants containing corticosteroids include agents, such as, e.g., fluocinolone and dexamethasone.

AT1 receptor antagonist refers to agents, such as DIOVAN.

ACE inhibitors include CIBACEN, benazepril, enazepril (LOTENSIN), captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, perindopril and trandolapril.

The term cyclooxygenase inhibitor, as used herein, includes, but is not limited to, e.g., Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (Celebrex), rofecoxib (Vioxx), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, e.g., 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid and lumiracoxib.

The term insulin-like growth factor receptor (IGF-R) refers to compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor 1 (IGF-1R), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the IGF-1R receptor, such as those compounds disclosed in WO 02/092599.

The term mTor kinase inhibitors refers to compounds which target, decrease or inhibit the activity/function of serine/theronine mTOR kinase are especially compounds, proteins or antibodies which target/inhibit members of the mTOR kinase family, e.g., RAD, RAD001, CCI-779, ABT578, SAR543, rapamycin and derivatives/analogs thereof, AP23573 and AP23841 from Ariad, everolimus (CERTICAN) and sirolimus.

"Somatostatin receptor antagonists", as used herein, refers to agents which target, treat or inhibit the somatostatin receptor, such as octreoride and SOM230.

Compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK and Ras/MAPK family members or PI(3) kinase family, or of the PI(3)-kinase-related kinase family and/or members of the cyclin-dependent kinase family (CDK) are especially those staurosporine derivatives disclosed in U.S. Patent No. 5,093,330, e.g., midostaurin; examples of further compounds include, e.g., UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds, such as those disclosed in WO 00/09495; FTIs; PD184352 or QAN697(a P13K inhibitor).

Comprised are likewise the corresponding stereoisomers, as well as the corresponding crystal modifications, e.g., solvates and polymorphs, which are disclosed therein. The compounds used as active ingredients in the combinations disclosed herein can be prepared and administered as described in the cited documents, respectively.

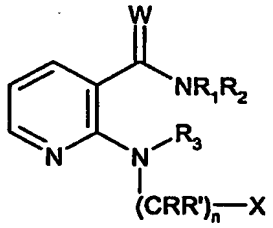
The structure of the active agents identified by code numberes, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International, e.g., IMS World Publications, or the publications mentioned above and below. The corresponding content thereof is hereby incorporated by reference.

It will be understood that references to the components (a) and (b) are meant to also include the pharmaceutically acceptable salts of any of the active substances. If active substances comprised by components (a) and/or (b) have, e.g., at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. Active substances having an acid group, e.g., COOH, can form salts with bases. The active substances comprised in components (a) and/or (b) or a pharmaceutically acceptable salts thereof may also be used in form of a hydrate or include other solvents used for crystallization. 2-[(Pyridin-6(*1H*)-on-3-yl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide is the most preferred combination partner (a).

The VEGF Inhibitor Compounds

Compounds which target, decrease or inhibit the activity of VEGFR are especially compounds, proteins or antibodies which inhibit or interact with at least one VEGF receptor tyrosine kinase, inhibit a VEGF receptor or bind to VEGF.

VEGF inhibitors for use in the present invention include those of formula (I)



(I)

wherein for formula (I) the variables are:

n is from 1 up to and including 6;

W is O or S;

R_1 and R_3 represent independently of each other hydrogen, lower alkyl or lower acyl;

R_2 represents an cycloalkyl group, an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

R and R' are independently of each other hydrogen or lower alkyl; and

X represents an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

or of a *N*-oxide or a possible tautomer thereof;

or of a pharmaceutically acceptable salt.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure for formula (I) the following meanings, unless otherwise indicated:

The prefix "lower" denotes a radical having up to and including a maximum of 7, especially up to and including a maximum of 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching.

Where the plural form is used for compounds, salts and the like, this is taken to mean also a single compound, salt or the like.

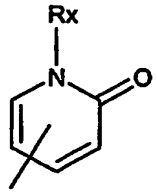
Any asymmetric carbon atoms, e.g., in compounds of formula (I), wherein R or R' is lower alkyl, may be present in the (*R*)-, (*S*)- or (*R,S*)-configuration, preferably in the (*R*)- or (*S*)-configuration. The compounds may thus be present as mixtures of isomers or as pure isomers, preferably as enantiomer-pure diastereomers.

The invention relates also to possible tautomers of the compounds of formula (I).

X is preferably pyridyl or phenyl, most preferred it is 3- or 4-pyridyl.

In a preferred embodiment of the invention, X is substituted by lower alkoxy.

In further a very preferred embodiment of the invention, X has the substructure X'



(X')

wherein Rx is hydrogen or lower alkyl.

R_2 is preferably phenyl which is mono- or disubstituted by lower alkyl, lower alkynyl, halogen, preferably fluoro, and trifluoromethyl; or cycloalkyl, preferably cyclohexyl substituted by lower alkyl, preferably *tert*-butyl.

R_3 is preferably hydrogen. W is preferably O. The integer n is preferably 1 or 2, very preferably 1.

Lower alkyl is preferably alkyl with from and including 1 up to and including 7, preferably from and including 1 to and including 5, and is linear or branched; preferably, lower alkyl is pentyl, such as *n*-pentyl, butyl, such as *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, propyl, such as *n*-propyl or isopropyl, ethyl or methyl. Preferably lower alkyl is methyl, propyl or *tert*-butyl.

Lower acyl is preferably formyl or acetyl.

"Aryl" is an aromatic radical which is bound to the molecule via a bond located at an aromatic ring carbon atom of the radical. In a preferred embodiment, aryl is an aromatic radical having 6-14 carbon atoms, especially phenyl, naphthyl, tetrahydronaphthyl, fluorenyl or phenanthrenyl, and is unsubstituted or substituted by one or more, preferably up to three, especially one or two substituents, especially selected from amino, mono- or disubstituted amino, halogen, lower alkyl, substituted alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, benzoyl, carbamoyl, *N*-mono- or *N,N*-disubstituted carbamoyl, amidino, guanidino, ureido, mercapto, sulfo, lower alkylthio, phenyl, phenoxy, phenylthio, phenyl-lower alkylthio, alkylphenylthio, lower alkylsulfinyl, phenylsulfinyl, phenyl-lower alkylsulfinyl, alkylphenylsulfinyl, lower alkanesulfonyl, phenylsulfonyl, phenyl-lower alkylsulfonyl, alkylphenylsulfonyl, halogen-lower alkylmercapto, halogen-lower alkylsulfonyl, such as especially trifluoromethane sulfonyl, dihydroxybora ($-B(OH)_2$), heterocyclyl, and lower alkylene dioxy bound at adjacent C-atoms of the ring, such as methylene dioxy. Aryl is more preferably phenyl or naphthyl, which in each case is either unsubstituted or independently substituted by one or two substituents selected from the group comprising halogen, especially fluorine, chlorine, or bromine; hydroxy; hydroxy, etherified by lower alkyl, e.g., methyl or by halogen-lower alkyl, e.g., trifluoromethyl; lower alkyl, e.g., methyl or propyl; lower alkynyl, such as 1-propynyl; esterified carboxy, especially lower alkoxy carbonyl, e.g., methoxy carbonyl, *n*-propoxy carbonyl or *iso*-propoxy carbonyl; *N*-mono-substituted carbamoyl, in particular, carbamoyl monosubstituted by lower alkyl, e.g., methyl, *n*-propyl or

iso-propyl; substituted alkyl, especially lower alkyl, e.g., methyl or ethyl, substituted by lower alkoxy carbonyl, e.g., methoxy carbonyl or ethoxy carbonyl; and halogen-lower alkyl, most preferably trifluoromethyl.

Aryl in the form of phenyl which is substituted by lower alkylene dioxy bound to two adjacent C-atoms, such as methylenedioxy, is preferably 3,4-methylenedioxyphenyl.

A cycloalkyl group is preferably cyclopentyl, cyclohexyl or cycloheptyl, and may be unsubstituted or substituted by one or more, especially one or two, substituents selected from the group defined above as substituents for aryl, most preferably by lower alkyl, such as methyl, lower alkoxy, such as methoxy or ethoxy, or hydroxy.

Substituted alkyl is alkyl as last defined, especially lower alkyl, preferably methyl; where one or more, especially up to three, substituents may be present, primarily from the group selected from halogen, especially fluorine, amino, *N*-lower alkylamino, *N,N*-di-lower alkylamino, *N*-lower alkanoylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl and phenyl-lower alkoxycarbonyl. Trifluoromethyl is especially preferred.

Mono- or disubstituted amino is especially amino substituted by one or two radicals selected independently of one another from lower alkyl, such as methyl; hydroxy-lower alkyl, such as 2-hydroxyethyl; phenyl-lower alkyl; lower alkanoyl, such as acetyl; benzoyl; substituted benzoyl, wherein the phenyl radical is especially substituted by one or more, preferably one or two, substituents selected from nitro, amino, halogen, *N*-lower alkylamino, *N,N*-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl and carbamoyl; and phenyl-lower alkoxycarbonyl, wherein the phenyl radical is unsubstituted or especially substituted by one or more, preferably one or two, substituents selected from nitro, amino, halogen, *N*-lower alkylamino, *N,N*-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl and carbamoyl; and is preferably *N*-lower alkylamino, such as *N*-methylamino, hydroxy-lower alkylamino, such as 2-hydroxyethylamino, phenyl-lower alkylamino, such as benzylamino, *N,N*-di-lower alkylamino, *N*-phenyl-lower alkyl-*N*-lower alkylamino, *N,N*-di-lower alkylphenylamino, lower alkanoylamino, such as acetylamino, or a substituent selected from the group comprising benzoylamino and phenyl-lower alkoxycarbonylamino, wherein the phenyl radical in each case is unsubstituted or especially substituted by nitro or amino, or also by halogen, amino, *N*-lower alkylamino, *N,N*-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl, carbamoyl or aminocarbonylamino.

Halogen is especially fluorine, chlorine, bromine, or iodine, especially fluorine, chlorine or bromine.

Etherified hydroxy is especially C_{8-20}alkyloxy, such as *n*-decyloxy, lower alkoxy (preferred), such as methoxy, ethoxy, isopropyloxy or *n*-pentyloxy, phenyl-lower alkoxy, such as benzyloxy, or also phenyloxy, or as an alternative or in addition to the previous group C_{8-20}alkyloxy, such as *n*-decyloxy, halogen-lower alkoxy, such as trifluoromethyloxy or 1,1,2,2-tetrafluoroethoxy.

Esterified hydroxy is especially lower alkanoyloxy, benzoyloxy, lower alkoxycarbonyloxy, such as *tert*-butoxycarbonyloxy or phenyl-lower alkoxycarbonyloxy, such as benzyloxycarbonyloxy.

Esterified carboxy is especially lower alkoxycarbonyl, such as tert-butoxycarbonyl, iso-propoxycarbonyl, methoxycarbonyl or ethoxycarbonyl, phenyl-lower alkoxycarbonyl or phenyloxycarbonyl.

Alkanoyl is primarily alkylcarbonyl, especially lower alkanoyl, e.g. acetyl.

N-Mono- or *N,N*-disubstituted carbamoyl is especially substituted by one or two substituents independently selected from lower alkyl, phenyl-lower alkyl and hydroxy-lower alkyl, at the terminal nitrogen atom.

Alkylphenylthio is especially lower alkylphenylthio.

Alkylphenylsulfonyl is especially lower alkylphenylsulfonyl.

Alkylphenylsulfinyl is especially lower alkylphenylsulfinyl.

A mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted refers to a heterocyclic moiety that is unsaturated in the ring binding the heteroaryl radical to the rest of the molecule in formula (I) and is preferably a ring, where at least in the binding ring, but optionally also in any annealed ring, one or more, preferably 1-4, most preferably 1 or 2, carbon atoms are replaced each by a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur; where the binding ring preferably has 5-12, more preferably 5-7 ring atoms; and may be unsubstituted or substituted by one or more, especially one or two,

substituents selected from the group defined above as substituents for aryl, most preferably by lower alkyl, such as methyl, lower alkoxy, such as methoxy or ethoxy, or hydroxy; preferably the mono- or bicyclic heteroaryl group is selected from *2H*-pyrrolyl, pyrrolyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, purinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, *4H*-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinnolinyl, pteridinyl, indolizinyl, *3H*-indolyl, indolyl, isoindolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, furazanyl and benzo[*d*]pyrazol. More preferably the mono- or bicyclic heteroaryl group is selected from the group consisting of pyrrolyl, benzimidazolyl, such as 1-benzimidazolyl, indazolyl, especially 5-indazolyl, pyridyl, especially 2-, 3- or 4-pyridyl, isoquinolinyl, especially 3-isoquinolinyl, quinolinyl, especially 4-quinolinyl, indolyl, especially 3-indolyl, thiazolyl or benzo[*d*]pyrazol. In one preferred embodiment of the invention the pyridyl radical is substituted by hydroxy in ortho position to the nitrogen atom and hence exists at least partially in the form of the corresponding tautomer which is pyridin-(*1H*)2-one.

Heterocyclyl is especially a 5- or 6-membered heterocyclic system with 1 or 2 heteroatoms selected from the group comprising nitrogen, oxygen and sulfur, which may be unsaturated or wholly or partly saturated, and is unsubstituted or substituted especially by lower alkyl, such as methyl; a radical selected from 2-methylpyrimidin-4-yl, oxazol-5-yl, 2-methyl-1,3-dioxolan-2-yl, *1H*-pyrazol-3-yl and 1-methyl-pyrazol-3-yl is preferred.

Salts are especially the pharmaceutically acceptable salts of compounds of formula (I).

Such salts are formed, e.g., as acid addition salts, preferably with organic or inorganic acids, from compounds of formula (I) with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, e.g., halogen acids, such as hydrochloric acid, sulfuric acid or phosphoric acid. Suitable organic acids are, e.g., carboxylic, phosphonic, sulfonic or sulfamic acids, e.g., acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or

4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, *N*-cyclohexylsulfamic acid, *N*-methyl-, *N*-ethyl- or *N*-propyl-sulfamic acid or other organic protonic acids, such as ascorbic acid.

High preference is given to a compound selected from the group consisting of:
2-[2-(4-Pyridyl)ethyl]amino-*N*-[3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(4-Pyridyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(2-Methyl-4-pyridyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(6-Methoxy-3-pyridyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(4-Pyridyl)methyl]amino-*N*-[3,4-bis(trifluoromethyl)-phenyl]-3-pyridinecarboxamide;
2-[(4-Pyridyl)methyl]amino-*N*-[5-fluoro-3-trifluoromethyl-phenyl]-3-pyridinecarboxamide;
2-[(4-Pyridyl)methyl]amino-*N*-(trans-4-*tert*-butyl-cyclohexane)-3-pyridinecarboxamide;
2-[(4-Pyridyl)methyl]amino-*N*-(4-*n*-propyl-phenyl)-3-pyridinecarboxamide;
2-[(4-Pyridyl)methyl]amino-*N*-(4-*n*-butyl-phenyl)-3-pyridinecarboxamide;
2-[(4-Pyridyl)methyl]amino-*N*-(4-*n*-pentyl-phenyl)-3-pyridinecarboxamide;
2-[(4-Pyridyl)methyl]amino-*N*-[4-(1-propynyl)-phenyl]-3-pyridinecarboxamide;
2-[(4-Pyridyl)methyl]amino-*N*-(5-indazolyl)-3-pyridinecarboxamide;
2-[(4-Pyridyl)methyl]amino-*N*-(3-isoquinolinyl)-3-pyridinecarboxamide;
2-[(Pyridin-6(*1H*)-on-3-yl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
and
the pharmaceutically acceptable salt thereof.

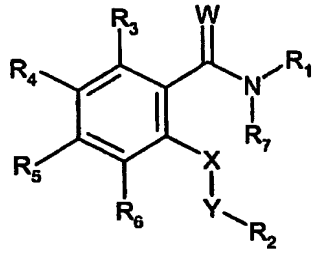
Furthermore, high preference is given to a compound selected from the group of compounds consisting of:
2-(Phenylmethylamino)-*N*-[3-(trifluoromethyl)phenyl]-3-pyridine-carboxamide, hydrochloride,
2-[(4-Pyridyl)methylamino]-*N*-[2-fluoro-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide,
2-[(4-Pyridyl)methylamino]-*N*-[4-bromo-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide,
2-[(4-Pyridyl)methylamino]-*N*-[2-methyl-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide,
2-[(4-Pyridyl)methylamino]-*N*-[2-methyl-5-(trifluoromethyl)phenyl]-3-pyridinecarboxamide,
2-[(4-Pyridyl)methylamino]-*N*-(*cis*-4-*tert*-butyl-cyclohexyl)-3-pyridinecarboxamide;
2-[(6-Methoxypyrid-3-yl)methylamino]-*N*-[4-bromo-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(6-Methoxypyrid-3-yl)methylamino]-*N*-[2-fluoro-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;

2-[(6-Methoxypyrid-3-yl)methylamino]-*N*-[2-methyl-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(1-Oxido-4-pyridyl)methylamino]-*N*-[3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[3-(*N*-methyl-carboxamido)phenyl]methylamino]-*N*-[3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(1-Methyl-pyridin-2(*1H*)-on-5-yl)methylamino]-*N*-[3-(trifluoromethyl)phenyl]-3-pyridine-carboxamide;
2-[(6-Methoxypyrid-3-yl)methylamino]-*N*-[4-propynyl-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(4-Pyridyl)methylamino]-*N*-[4-propynyl-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(Pyridin-2(*1H*)-on-5-yl)methyl]amino-*N*-[4-propynyl-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(Pyridin-2(*1H*)-on-5-yl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(3-Hydroxyphenyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(Pyridin-2(*1H*)-on--5-yl)methyl]amino-*N*-[4-bromo-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(Pyridin-2(*1H*)-on-5-yl)methyl]amino-*N*-[2-fluoro-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(Pyridin-2(*1H*)-on-5-yl)methyl]amino-*N*-[2-methyl-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(Pyridin-2(*1H*)-on--5-yl)methyl]amino-*N*-[4-propyl-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(6-Methoxypyrid-3-yl)methylamino]-*N*-[4-propyl-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(4-Pyridyl)methyl]amino-*N*-[4-(*n*-propyl)-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(4-Pyridyl)methyl]amino-*N*-(5-thiazolyl)-3-pyridinecarboxamide;
2-[(4-Hydroxyphenyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]-3-pyridine-carboxamide;
2-[(4-Pyridyl)methyl]amino-*N*-(benzo[*d*]pyrazol-5-yl)-3-pyridinecarboxamide;
2-[(6-Methoxy-3-pyridyl)methyl]amino-*N*-(3-isoquinolinyl)-3-pyridinecarboxamide;
2-[(6-Methoxy-3-pyridyl)methyl]amino-*N*-(benzo[*d*]pyrazol-5-yl)-3-pyridinecarboxamide;
2-[(Pyridin-2(*1H*)-on-5-yl)methyl]amino-*N*-(3-isoquinolinyl)-3-pyridinecarboxamide;
2-[(Pyridin-2(*1H*)-on-5-yl)methyl]amino-*N*-(benzo[*d*]pyrazol-5-yl)-3-pyridinecarboxamide;
2-[(Pyridin-2(*1H*)-on-5-yl)methyl]amino-*N*-(*cis*-4-*tert*-butyl-cyclohexyl)-3-pyridinecarboxamide;
2-[(Pyridin-2(*1H*)-on-5-yl)methyl]amino-*N*-(*trans*-4-*tert*-butyl-cyclohexyl)-3-pyridinecarboxamide;

2-[(1-Oxido-4-pyridyl)methylamino]-*N*-[4-propyl-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(Pyridin-2(*1H*)-on-5-yl)methyl]amino-*N*-[4-ethyl-3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(Pyridin-2(*1H*)-on-5-yl)methyl]amino-*N*-[3,4-*bis*(trifluoromethyl)phenyl]-3-pyridinecarboxamide;
2-[(1-Methyl-pyridin-2(*1H*)-on-5-yl)methylamino]-*N*-[3,4-*bis*(trifluoromethyl)-phenyl]-3-pyridinecarboxamide; and
the pharmaceutically acceptable salts thereof.

VEGF inhibitors of formula (I) and their preparation are disclosed in WO 01/55114, published August 2, 2001, which is incorporated herein in its entirety.

Other VEGF inhibitors include compounds of formula (II)



(II)

wherein the substituents for compounds of formula (II) are:

W is O or S;

X is NR_8;

Y is CR_9R_{10}-$(CH_2)_n$, wherein

R_9 and R_{10} are independently of each other hydrogen or lower alkyl; and

n is an integer of from and including 0 to and including 3; or

Y is SO_2;

R_1 is aryl;

R_2 is a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms with the exception that R_2 cannot represent 2-phthalimidyl, and in case of Y = SO_2 cannot represent 2,1,3-benzothiadiazol-4-yl;

any of R_3, R_4, R_5 and R_6, independently of the other, is H or a substituent other than hydrogen; and

R_7 and R_8, independently of each other, are H or lower alkyl;

or a *N*-oxide or a pharmaceutically acceptable salt thereof.

The general terms used hereinbefore and hereinafter preferably have, within the context of formula (II) the following meanings, unless otherwise indicated.

The prefix "lower" denotes a radical having up to and including a maximum of 7, especially up to and including a maximum of 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching.

Where the plural form is used for compounds, salts and the like, this is taken to mean also a single compound, salt or the like.

Any asymmetric carbon atoms, e.g., in compounds of formula (II), wherein R_9 is lower alkyl, may be present in the (*R*)-, (*S*)- or (*R,S*)-configuration, preferably in the (*R*)- or (*S*)-configuration. The compounds may thus be present as mixtures of isomers or as pure isomers, preferably as enantiomer-pure diastereomers.

The invention relates also to possible tautomers of the compounds of formula (II).

Lower alkyl is preferably alkyl with from and including 1 up to and including 7, preferably from and including 1 to and including 4, and is linear or branched; preferably, lower alkyl is butyl, such as *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl; propyl, such as *n*-propyl or isopropyl; ethyl; or preferably methyl.

The index n is preferably 0 or 1, especially 0.

Y is preferably methylene (CH_2) or ethylene (CH_2-CH_2), most preferably methylene.

"Aryl" is an aromatic radical which is bound to the molecule via a bond located at an aromatic ring carbon atom of the radical. In a preferred embodiment, aryl is an aromatic radical having 6-14 carbon atoms, especially phenyl, naphthyl, tetrahydronaphthyl, fluorenyl or phenanthrenyl, and is unsubstituted or substituted by one or more, preferably up to three, especially one or two substituents, especially selected from amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, benzoyl, carbamoyl, *N*-mono- or *N,N*-disubstituted carbamoyl, amidino, guanidino, ureido, mercapto, sulfo, lower alkylthio, phenyl, phenoxy, phenylthio, phenyl-lower alkylthio, alkylphenylthio, lower alkylsulfinyl, phenylsulfinyl, phenyl-lower alkylsulfinyl, alkylphenylsulfinyl, lower alkanesulfonyl,

phenylsulfonyl, phenyl-lower alkylsulfonyl, alkylphenylsulfonyl, lower alkenyl, lower alkanoyl, halogen-lower alkylmercapto, halogen-lower alkylsulfonyl, such as especially trifluoromethane sulfonyl, dihydroxybora (-$B(OH)_2$), heterocyclyl, and lower alkylene dioxy bound at adjacent C-atoms of the ring, such as methylene dioxy; aryl is preferably phenyl or naphthyl, which in each case is either unsubstituted or independently substituted by one or two substituents selected from the group comprising halogen, especially fluorine, chlorine or bromine; hydroxy; hydroxy, etherified by lower alkyl, e.g., methyl, or by halogen-lower alkyl, e.g., trifluoromethyl; esterified carboxy, especially lower alkoxy carbonyl, e.g., methoxy carbonyl, *n*-propoxy carbonyl or *iso*-propoxy carbonyl; *N*-mono-substituted carbamoyl, in particular, carbamoyl monosubstituted by lower alkyl, e.g., methyl, *n*-propyl or *iso*-propyl; lower alkyl, especially methyl, ethyl or propyl; substituted alkyl, especially lower alkyl, e.g., methyl or ethyl, substituted by lower alkoxy carbonyl, e.g., methoxy carbonyl or ethoxy carbonyl; halogen-lower alkyl, especially trifluoromethyl; lower alkylsulfinyl, such as methylsulfinyl, and lower alkanesulfonyl, such as methane sulfonyl. Aryl is preferably 3- or 4-chlorophenyl, 3-bromophenyl, 4-phenoxyphenyl, 2, 3- or 4-methylphenyl, 4-methoxyphenyl, 3- or 4-*tert*-butylphenyl, 4-*n*-propylphenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 3-trifluoromethoxyphenyl, 3,4-(trifluoromethyl)phenyl, 3-fluoro-4-methylphenyl, 3-chloro-4-methylphenyl, 4-chloro-3-trifluoromethylphenyl, 3-chloro-5-trifluoromethylphenyl, 4-methylsulfinylphenyl, 4-methanesulfonylphenyl, 4-biphenyl, naphthyl, 2-naphthyl; tetrahydronaphthyl, in particular, 5,6,7,8-tetrahydronaphthyl; hydroxynaphthyl, in particular, 7-hydroxynaphthyl, 8-hydroxynaphthyl or 8-hydroxy-2-naphthyl; methoxynaphthyl, in particular, 4-methoxy-2-naphthyl; halonaphthyl, in particular, 4-chloronaphthyl or 3-bromo-2-naphthyl.

Mono- or disubstituted amino is especially amino substituted by one or two radicals selected independently of one another from lower alkyl, such as methyl; hydroxy-lower alkyl, such as 2-hydroxyethyl; phenyl-lower alkyl; lower alkanoyl, such as acetyl; benzoyl; substituted benzoyl, wherein the phenyl radical is especially substituted by one or more, preferably one or two, substituents selected from nitro, amino, halogen, *N*-lower alkylamino, *N,N*-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl and carbamoyl; and phenyl-lower alkoxycarbonyl, wherein the phenyl radical is unsubstituted or especially substituted by one or more, preferably one or two, substituents selected from nitro, amino, halogen, *N*-lower alkylamino, *N,N*-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl and carbamoyl; and is preferably *N*-lower alkylamino, such as *N*-methylamino, hydroxy-lower alkylamino, such as

2-hydroxyethylamino, phenyl-lower alkylamino, such as benzylamino, *N,N*-di-lower alkylamino, *N*-phenyl-lower alkyl-*N*-lower alkylamino, *N,N*-di-lower alkylphenylamino, lower alkanoylamino, such as acetylamino or a substituent selected from the group comprising benzoylamino and phenyl-lower alkoxycarbonylamino, wherein the phenyl radical in each case is unsubstituted or especially substituted by nitro or amino, or also by halogen, amino, *N*-lower alkylamino, *N,N*-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl, carbamoyl or aminocarbonylamino.

Halogen is especially fluorine, chlorine, bromine or iodine, especially fluorine, chlorine or bromine.

In the preferred embodiment, alkyl has up to a maximum of 12 carbon atoms and is especially lower alkyl, especially methyl, or also ethyl, *n*-propyl, isopropyl or *tert*-butyl.

Substituted alkyl is alkyl as last defined, especially lower alkyl, preferably methyl; where one or more, especially up to three, substituents may be present, primarily from the group selected from halogen, especially fluorine, amino, *N*-lower alkylamino, *N,N*-di-lower alkylamino, *N*-lower alkanoylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl and phenyl-lower alkoxycarbonyl. Trifluoromethyl is especially preferred.

Etherified hydroxy is especially C_{8-20}alkyloxy, such as *n*-decyloxy; lower alkoxy (preferred), such as methoxy, ethoxy, isopropyloxy or *n*-pentyloxy; phenyl-lower alkoxy, such as benzyloxy; or also phenyloxy, or as an alternative or in addition to the previous group C_{8-20}alkyloxy, such as *n*-decyloxy; halogen-lower alkoxy, such as trifluoromethyloxy or 1,1,2,2-tetrafluoroethoxy.

Esterified hydroxy is especially lower alkanoyloxy, benzoyloxy, lower alkoxycarbonyloxy, such as *tert*-butoxycarbonyloxy; or phenyl-lower alkoxycarbonyloxy, such as benzyloxycarbonyloxy.

Esterified carboxy is especially lower alkoxycarbonyl, such as *tert*-butoxycarbonyl, *iso*-propoxycarbonyl, methoxycarbonyl or ethoxycarbonyl, phenyl-lower alkoxycarbonyl or phenyloxycarbonyl.

Alkanoyl is primarily alkylcarbonyl, especially lower alkanoyl, e.g., acetyl.

N-mono- or *N,N*-disubstituted carbamoyl is especially substituted by one or two substituents independently selected from lower alkyl, phenyl-lower alkyl, and hydroxy-lower alkyl, at the terminal nitrogen atom.

Alkylphenylthio is especially lower alkylphenylthio.

Alkylphenylsulfonyl is especially lower alkylphenylsulfonyl.

Alkylphenylsulfinyl is especially lower alkylphenylsulfinyl.

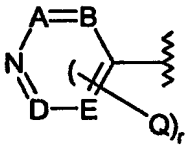
Heterocyclyl is especially a 5- or 6-membered heterocyclic system with 1 or 2 heteroatoms selected from the group comprising nitrogen, oxygen and sulfur, which may be unsaturated or wholly or partly saturated, and is unsubstituted or substituted especially by lower alkyl, such as methyl; a radical selected from 2-methylpyrimidin-4-yl, oxazol-5-yl, 2-methyl-1,3-dioxolan-2-yl, *1H*-pyrazol-3-yl and 1-methyl-pyrazol-3-yl is preferred.

Aryl in the form of phenyl which is substituted by lower alkylene dioxy bound to two adjacent C-atoms, such as methylenedioxy, is preferably 3,4-methylenedioxyphenyl.

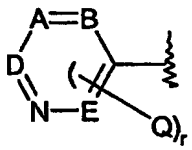
Heteroaryl refers to a heterocyclic moiety that is unsaturated in the ring binding the heteroaryl radical to the rest of the molecule in formula (II) and is preferably mono-, bi- or tricyclic, preferably mono- or bicyclic; where at least in the binding ring, but optionally also in any annealed ring, one or more, preferably 1-4, most preferably 3 or 4, carbon atoms are replaced each by a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur; where the binding ring preferably has 5-12, more preferably 5-7 ring atoms; and may be unsubstitued or substituted by one or more, especially one or two, substituents selected from the group defined above as substituents for aryl, most preferably by lower alkyl, such as methyl; preferably heteroaryl is selected from thienyl, furyl, pyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, *2H*-pyrrolyl, pyrrolyl, lower-alkyl substituted imidazolyl, benzimidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, *3H*-indolyl, indolyl, indazolyl, triazolyl, tetrazolyl, purinyl, *4H*-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl and furazanyl; more preferably selected from the group consisting of triazolyl, especially 1,2,4-triazolyl, 1,2,3-triazolyl or 1,3,4-triazolyl; pyridyl, especially 2-, 3- or 4-pyridyl; indolyl, especially 3-indolyl; lower-alkylthiazolyl, especially 2-(4-methylthiazolyl); pyrrolyl, especially 1-pyrrolyl; lower alkylimidazolyl, especially

4-(1-methylimidazolyl), 4-(2-methylimidazolyl) or 4-(5-methylimidazolyl); benzimidazolyl, such as 1-benzimidazolyl; or tetrazolyl, such as 5-(1,2,3,4-tetrazolyl).

A mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms is preferably a heteroaryl group as defined above for heteroaryl, with the proviso that preferably at least one nitrogen is present as ring heteroatom in the binding ring (that is, the ring from which the bond starts that binds the heteroaryl moiety to the rest of the molecule) and with the exception that R_2 cannot represent 2-phthalimidyl, and in case of Y = SO_2R_2 cannot represent 2,1,3-benzothiadiazol-4-yl. Preferred is imidazolyl, especially imidazol-4-yl; quinolyl, especially 3-, 4-, 5-quinolyl; naphthyridinyl, especially 3-(1,8-naphthyridinyl) or 4-(1,8-naphthyridinyl); or especially a moiety of the formula (IIb) or (IIc)



(IIb) or



(IIc)

wherein

r is 0-2;

A, B, D and E are, independently of one another, N or CH, with the stipulation that not more than 2 of these radicals are N; preferably, each of A, B, D and E is CH; and

Q is lower alkyl, especially methyl, hydroxy, lower alkoxy, especially methoxy, lower thioalkyl, especially methylthio, or halogen, especially fluoro, chloro or bromo.

Very preferably R_2 is 3-pyridyl, 4-pyridyl, 4-quinolinyl or 5-quinolinyl. Most preferably, R_2 is 4-pyridyl.

A substituent other than hydrogen is preferably selected from amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, *N*-mono- or *N,N*-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, lower alkylthio, phenylthio, phenyl-lower alkylthio, alkylphenylthio, lower alkylsulfinyl, phenylsulfinyl, phenyl-lower alkylsulfinyl, alkylphenylsulfinyl, lower alkanesulfonyl, phenylsulfonyl, phenyl-lower alkylsulfonyl, alkylphenylsulfonyl, lower alkenyl, lower alkanoyl, halogen-lower alkylmercapto, halogen-lower alkylsulfonyl, such as especially trifluoromethane sulfonyl and heterocyclyl. Two substitutents other than hydrogen bound at adjacent C-atoms of the ring can also represent lower alkylene dioxy, such as methylene dioxy ethylene dioxy.

Preferably, a substituent other than hydrogen is lower alkyl or halogen, especially methyl, chloro or fluoro.

Preferably, R_7 and R_8 are hydrogen, and R_3, R_4, R_5 and R_6 each are independently hydrogen, chloro or fluorine.

Salts are especially the pharmaceutically acceptable salts of compounds of formula (II).

Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula (II)with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, e.g., halogen acids, such as hydrochloric acid, sulfuric acid or phosphoric acid. Suitable organic acids are, e.g., carboxylic; phosphonic; sulfonic or sulfamic acids, e.g., acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid or citric acid; amino acids, such as glutamic acid or aspartic acid; maleic acid; hydroxymaleic acid; methylmaleic acid; cyclohexanecarboxylic acid; adamantanecarboxylic acid; benzoic acid; salicylic acid; 4-aminosalicylic acid; phthalic acid; phenylacetic acid; mandelic acid; cinnamic acid; methane- or ethane-sulfonic acid; 2-hydroxyethanesulfonic acid; ethane-1,2-disulfonic acid; benzenesulfonic acid; 2-naphthalenesulfonic acid; 1,5-naphthalene-disulfonic acid; 2-, 3- or 4-methylbenzenesulfonic acid; methylsulfuric acid; ethylsulfuric acid; dodecylsulfuric acid; *N*-cyclohexylsulfamic acid; *N*-methyl-; *N*-ethyl- or *N*-propyl-sulfamic acid; or other organic protonic acids, such as ascorbic acid.

High preference is given to a compound selected from:
2-[(4-Pyridyl)methyl]amino-*N*-(4-trifluoromethylphenyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(4-chlorophenyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(4-methylphenyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(3-fluoro-4-methylphenyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(4-chloro-3-trifluoromethylphenyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(3-chloro-5-trifluoromethylphenyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(4-methylphenyl)-6-methylbenzamide; and
2-[(4-Quinolyl)methyl]amino-*N*-(4-chlorophenyl)benzamide;
or a pharmaceutically acceptable salt thereof.

Furthermore, high preference is given to a compound selected from:

2-[(4-Pyridyl)methyl]amino-*N*-[3-fluoro-(4-trifluoromethyl)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-phenylbenzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[4-fluoro-3-(trifluoromethyl)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[3-fluoro-5-(trifluoromethyl)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[3,5-(*bis*trifluoromethyl)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[3,4-*bis*-(trifluoromethyl)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[3-methoxy-5-(trifluoromethyl)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[3-(1,1-dimethylethyl)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-(3-cyanophenyl)benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[(3-methylthio)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-(3-acetylaminophenyl)benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[3-[(aminocarbonyl)amino]phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[3-(dimethylamino)phenyl]benzamide;

5-Methoxy-2-[(4-pyridyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]benzamide;

3-Methyl-2-[(4-pyridyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]benzamide;

4,5-Difluoro-2-[(4-pyridyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N'*-methyl-*N'*-[3-(trifluoromethyl)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[(3-methylsulphonyl)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[(3-methylsulphinyl)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[4-(1,1-dimethylethyl)phenyl]benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-(3-chlorophenyl)benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-(3-bromophenyl)benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-(3-methylphenyl)benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-(3-benzoylphenyl)benzamide;

2-[(4-Pyridyl)methyl]amino-*N*-[3-(aminocarbonyl)phenyl]benzamide;

2-[(3-Pyridyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]benzamide;

2-[(4-Quinolinyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]benzamide;

2-[(5-Quinolinyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]benzamide;

2-[(4-(2-Methyl)pyridyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]benzamide;

2-[(4-(1,2-Dihydro-2-oxo)pyridyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]-benzamide;

2-[(4-Quinolinyl)methyl]amino-*N*-(4-chlorophenyl)benzamide;

2-[(2-Imidazolyl)methyl]amino-*N*-(4-chlorophenyl)benzamide;

2-[2-(4-Pyridyl)ethyl]amino-*N*-[3-(trifluoromethyl)phenyl]benzamide;

2-[2-(3-Pyridyl)ethyl]amino-*N*-[3-(trifluoromethyl)phenyl]benzamide;
2-[1-Methyl-2-(3-pyridyl)ethyl]amino-*N*-[3-(trifluoromethyl)phenyl]benzamide;
2-[(1-Oxido-4-pyridyl)methyl]amino-*N*-[3-(trifluoromethyl)phenyl]benzamide; and
2-[(4-Pyridyl)methyl]methylamino-*N*-[3-(trifluoromethyl)phenyl]benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(4-chloronaphthyl)benzamide;
6-Methyl-2-[(4-pyridyl)methyl]amino-*N*-(4-chlorophenyl)benzamide;
6-Chloro-2-[(4-pyridyl)methyl]amino-*N*-(4-chlorophenyl)benzamide;
3,4-Methylendioxy-6-[(4-pyridyl)methyl]amino-*N*-(4-chlorophenyl)benzamide;
4,5-Dimethyl-2-[(4-pyridyl)methyl]amino-*N*-(4-chlorophenyl)benzamide;
5-Chloro-2-[(4-pyridyl)methyl]amino-*N*-(4-*n*-propylphenyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(4-*n*-propylphenyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(7-hydroxynaphthyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(8-hydroxy-2-naphthyl)benzamide;
4-Chloro-2-[(4-pyridyl)methyl]amino-*N*-(4-chlorophenyl)benzamide;
5-Methyl-2-[(4-pyridyl)methyl]amino-*N*-(4-chlorophenyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(5,6,7,8-tetrahydronaphthyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(4-biphenyl)benzamide;
5-Chloro-2-[(4-pyridyl)methyl]amino-*N*-(4-chlorophenyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(naphthyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(2-napthyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(4-methoxyphenyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-[3-(trifluoromethoxy)phenyl]benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(4-methoxy-2-naphthyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(3-bromo-2-naphthyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-[4-(isopropoxycarbonyl)phenyl]benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-[4-(trifluoromethoxy)phenyl]benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-[4-(isopropylcarbamoyl)phenyl]benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(3-chloro-4-methylphenyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(2-methylphenyl)benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-[3-(methoxycarbonylmethyl)phenyl]benzamide;
2-[(4-Pyridyl)methyl]amino-*N*-(4-phenoxyphenyl)benzamide;
or a pharmaceutically acceptable salt thereof.

Compounds of formula (II), and their preparation, are disclosed in WO 00/27820 published May 18, 2000 and U.S. Patent No. 6,448,277, both of which are incorporated herein in their entirety.

Other VEGF inhibitors suitable for use in the present invention include the 4-pyridylmethyl-phthalazine derivatives which are described in U.S. Patent No. 6,258,812, which is here incorporated by reference. Also included are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 98/35958, e.g., 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g., the succinate, or in WO 00/09495, WO 00/59509, WO 98/11223, WO 00/27819 and EP 0 769 947; those as described by Prewett et al., *Cancer Res*, Vol. 59, pp. 5209-5218 (1999); Yuan et al., *Proc Natl Acad Sci USA*, Vol. 93, pp. 14765-14770 (1996); Zhu et al., *Cancer Res*, Vol. 58, pp. 3209-3214 (1998); and Mordenti et al., *Toxicol Pathol*, Vol. 27, No. 1, pp 14-21 (1999); in WO 00/37502 and WO 94/10202; ANGIOSTATIN, described by O'Reilly et al., *Cell*, Vol. 79, pp. 315-328 (1994); ENDOSTATIN, described O'Reilly et al., *Cell*, Vol. 88, pp. 277-285 (1997); anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, e.g., rhuMAb and RHUFab; VEGF aptamer, e.g., Macugon; FLT-4 inhibitors; and FLT-3 inhibitors. Monoclonal antibodies of VEGFR.

Other VEGF inhibitors include HuMV833, IMC-1C11a VEGFR-2 IgG1 antibody, Angiozyme (RPI 4610), Vatalanib (PTK787/zk 222584), SU11248, ZD6474, CEP-7055, CP-547-632, GW2286 and PD-173074.

The Combinations

Thus, in a first aspect, the present invention relates to a method of preventing or treating diseases triggered by diseases characterized by cell proliferation and inflammation, coronary disease, hypertension, renal diseases, diabetes, and ocular diseases and conditions in a mammal, preferably a human patient, which comprises treating the patient concurrently or sequentially with pharmaceutically effective amounts of a combination of:

(a) a VEGF inhibitor compound, preferably of formula (I) or (II); and

(b) a second therapeutic agent.

In another aspect, the present invention relates to a pharmaceutical composition comprising a combination of:

(a) a VEGF inhibitor compound, preferably of formula (I) or (II); and

(b) a second therapeutic agent.

In a yet further aspect, the present invention provides a pharmaceutical preparation comprising:

(a) a VEGF inhibitor compound of formula (I) or (II); and

(b) one or more second therapeutic agents, together with a pharmaceutically acceptable carrier.

In preferred embodiment, the present invention provides a pharmaceutical preparation comprising:

(a) a VEGF inhibitor compound of formula (I) or (II); and

(b) one or more second therapeutic agents selected from the group consisting of angiostatic steroids, photodynamic therapy, implants containing corticosteroids, AT1 receptor antagonists, ACE inhibitors, cyclooxygenase inhibitors, IGR-1R inhibitors, mTOR kinase inhibitors, somatostatin receptor antagonists, PI3K inhibitors, Raf kinase inhibitors and PKC inhibitors.

In another preferred embodiment, the present invention provides a pharmaceutical preparation comprising:

(a) a VEGF inhibitor compound of formula (I) or (II); and

(b) one or more second therapeutic agents selected from the group consisting of VISUDYNE, PREXIGE, CELEBREX, VIOXX, RAD001, SOM230, octreotide, QAN697, anecortave, triamcinolone, fluocinolone, dexamethasone, DIOVAN and CIBACEN.

Any of the combination of components (a) and (b), the method of treating a warm-blooded animal comprising administering these two components, a pharmaceutical composition comprising these two components for simultaneous, separate or sequential use, the use of the combination for the delay of progression or the treatment of a proliferative disease or for the manufacture of a pharmaceutical preparation for these purposes or a commercial product comprising such a combination of components (a) and (b), all as mentioned or defined above, will be referred to subsequently also as COMBINATION OF

THE INVENTION (so that this term refers to each of these embodiments which thus can replace this term where appropriate).

Simultaneous administration may, e.g., take place in the form of one fixed combination with two or more active ingredients, or by simultaneously administering two or more active ingredients that are formulated independently. Sequential use (administration) preferably means administration of one (or more) components of a combination at one time point, other components at a different time point, that is, in a chronically staggered manner, preferably such that the combination shows more efficiency than the single compounds administered independently (especially showing synergism). Separate use (administration) preferably means administration of the components of the combination independently of each other at different time points, preferably meaning that the components (a) and (b) are administered such that no overlap of measurable blood levels of both compounds are present in an overlapping manner (at the same time).

Also combinations of two or more of sequential, separate and simultaneous administration are possible, preferably such that the combination component-drugs show a joint therapeutic effect that exceeds the effect found when the combination component-drugs are used independently at time intervals so large that no mutual effect on their therapeutic efficiency can be found, a synergistic effect being especially preferred.

"Jointly therapeutically active" or "joint therapeutic effect" means that the compounds may be given separately (in a chronically staggered manner, especially a sequence-specific manner) in such time intervals that they preferably, in the warm-blooded animal, especially human, to be treated, still show a (preferably synergistic) interaction (joint therapeutic effect). Whether this is the case, can *inter alia* be determined by following the blood levels, showing that both compounds are present in the blood of the human to be treated at least during certain time intervals.

"Pharmaceutically effective" preferably relates to an amount that is therapeutically or in a broader sense also prophylactically effective against the progression of a disease.

The term "a commercial package" or "a product", as used herein, defines especially a 'kit of parts" in the sense that the components (a) and (b) as defined above can be dosed independently or by use of different fixed combinations with distinguished amounts of the components (a) and (b), i.e., simultaneously or at different time points. Moreover, these

terms comprise a commercial package comprising (especially combining) as active ingredients components (a) and (b), together with instructions for simultaneous, sequential (chronically staggered, in time-specific sequence, preferentially) or (less preferably) separate use thereof in the delay of progression or treatment of a proliferative disease. The parts of the kit of parts can then, e.g., be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Very preferably, the time intervals are chosen such that the effect on the treated disease in the combined use of the parts is larger than the effect which would be obtained by use of only any one of the combination partners (a) and (b) (as can be determined according to standard methods. The ratio of the total amounts of the combination partner (a) to the combination partner (b) to be administered in the combined preparation can be varied, e.g., in order to cope with the needs of a patient sub-population to be treated or the needs of the single patient which different needs can be due to the particular disease, age, sex, body weight, etc. of the patients. Preferably, there is at least one beneficial effect, e.g., a mutual enhancing of the effect of the combination partners (a) and (b), in particular, a more than additive effect, which hence could be achieved with lower doses of each of the combined drugs, respectively, than tolerable in the case of treatment with the individual drugs only without combination, producing additional advantageous effects, e.g., less side effects or a combined therapeutic effect in a non-effective dosage of one or both of the combination partners (components) (a) and (b), and very preferably a strong synergism of the combination partners (a) and (b).

Both in the case of the use of the combination of components (a) and (b) and of the commercial package, any combination of simultaneous, sequential and separate use is also possible, meaning that the components (a) and (b) may be administered at one time point simultaneously, followed by administration of only one component with lower host toxicity either chronically, e.g., more than 3-4 weeks of daily dosing, at a later time point and subsequently the other component or the combination of both components at a still later time point (in subsequent drug combination treatment courses for an optimal anti-tumor effect) or the like.

The COMBINATION OF THE INVENTION can also be applied in combination with other treatments, e.g., surgical intervention, hyperthermia and/or irradiation therapy.

The pharmaceutical compositions according to the present invention can be prepared by conventional means and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals including man, comprising a therapeutically effective amount of a VEGF inhibitor and at least one therapeutic agent alone or in combination with one or more pharmaceutically acceptable carriers, especially those suitable for enteral or parenteral application.

The pharmaceutical compositions comprise from about 0.00002% to about 100%, especially, e.g., in the case of infusion dilutions that are ready for use, of 0.0001-0.02%, or, e.g., in case of injection or infusion concentrates or especially parenteral formulations, from about 0.1% to about 95%, preferably from about 1% to about 90%, more preferably from about 20% to about 60%, active ingredient (weight by weight, in each case). Pharmaceutical compositions according to the invention may be, e.g., in unit dose form, such as in the form of ampoules, vials, dragées, tablets, infusion bags or capsules.

The effective dosage of each of the combination partners employed in a formulation of the present invention may vary depending on the particular compound or pharmaceutical compositions employed, the mode of administration, the condition being treated and the severity of the condition being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the condition.

Pharmaceutical preparations for the combination therapy for enteral or parenteral administration are, e.g., those in unit dosage forms, such as sugar-coated tablets, capsules or suppositories, and furthermore ampoules. If not indicated otherwise, these formulations are prepared by conventional means, e.g., by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. It will be appreciated that the unit content of a combination partner contained in an individual dose of each dosage form need not in itself constitute an effective amount since the necessary effective amount can be reached by administration of a plurality of dosage units. One of skill in the art has the ability to determine appropriate pharmaceutically effective amounts of the combination components.

Preferably, the compounds or the pharmaceutically acceptable salts thereof, are administered as an oral pharmaceutical formulation in the form of a tablet, capsule or syrup; or as parenteral injections, if appropriate.

In preparing compositions for oral administration, any pharmaceutically acceptable media may be employed, such as water, glycols, oils, alcohols, flavoring agents, preservatives and coloring agents. Pharmaceutically acceptable carriers include starches, sugars, microcrystalline celluloses, diluents, granulating agents, lubricants, binders and disintegrating agents.

Solutions of the active ingredient, and also suspensions, and especially isotonic aqueous solutions or suspensions, are useful for parenteral administration of the active ingredient, it being possible, e.g., in the case of lyophilized compositions that comprise the active ingredient alone or together with a pharmaceutically acceptable carrier, e.g., mannitol, for such solutions or suspensions to be produced prior to use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, e.g., preservatives, stabilizers, wetting and/or emulsifying agents, solubilizers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known *per se*, e.g., by means of conventional dissolving or lyophilizing processes. The solutions or suspensions may comprise viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin. Suspensions in oil comprise as the oil component the vegetable, synthetic or semi-synthetic oils customary for injection purposes.

The isotonic agent may be selected from any of those known in the art, e.g., mannitol, dextrose, glucose and sodium chloride. The infusion formulation may be diluted with the aqueous medium. The amount of aqueous medium employed as a diluent is chosen according to the desired concentration of active ingredient in the infusion solution. Infusion solutions may contain other excipients commonly employed in formulations to be administered intravenously, such as antioxidants.

The present invention further relates to "a combined preparation", which, as used herein, defines especially a "kit of parts" in the sense that the combination partners (a) and (b) as defined above can be dosed independently or by use of different fixed combinations with distinguished amounts of the combination partners (a) and (b), i.e., simultaneously or at different time points. The parts of the kit of parts can then, e.g., be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. The ratio of the total amounts of the combination partner (a) to the combination partner (b) to be administered in the combined preparation can be varied, e.g., in order to cope with the needs of a patient sub-population to

be treated or the needs of the single patient based on the severity of any side effects that the patient experiences.

The present invention especially relates to a combined preparation, which comprises:

(a) one or more unit dosage forms of a VEGF inhibitor; and

(b) one or more unit dosage forms of a second therapeutic agent.

The Diseases to be Treated

The compositions of the present invention are useful for treating or preventing diseases characterized by cell proliferation and inflammation, coronary disease, hypertension, renal diseases, diabetes, ocular diseases and conditions in a mammal.

The combination of the present invention can also be used to prevent or treat diseases that are triggered by persistent angiogenesis, such as psoriasis and restenosis, e.g., stent-induced restenosis; endometriosis; Crohn's disease; arthritis, such as rheumatoid arthritis; hemangioma; angiofibroma; ocular diseases, such as exudative form of age-related macular degeneration (Wet AMD), age-related macular degeneration (Dry AMD), macular edema, diabetic macular edema (DME), cystoid macular edema (CME), diabetic reinopathy, proliferative diabetic retinopathy (PDR), ischemic retinopathy, choroidal neovascularization, retinal neovascularization, retinitis pigmentosa (RP) and pathologic myopia.

Also included are renal diseases, such as glomerulonephritis; diabetic nephropathy; malignant nephrosclerosis; thrombotic microangiopathic syndromes; transplant rejections and glomerulopathy; fibrotic diseases, such as cirrhosis of the liver; mesangial cell-proliferative diseases; arteriosclerosis; injuries of the nerve tissue and for inhibiting the reocclusion of vessels after balloon catheter treatment, for use in vascular prosthetics or after inserting mechanical devices for holding vessels open, such as, e.g., stents, as immunosuppressants, as an aid in scar-free wound healing, and for treating age spots and contact dermatitis.

Combinations of the present invention include use for the treatment, prevention or inhibition of diseases characterized by cell proliferation and infiltration of inflammatory cells such as inflammation, RHA, asthma, chronic bronchitis, artheroschlerosis and transplant rejection.

The combinations are also useful for anti-VEGF therapy, such as treating, preventing and inhibiting rheumatoid arthritis; ocular, e.g., neovascular diseases; and psoriasis. The combinations can also be used as VEGFR-3 inhibitors in lymphangiogenesis.

As used herein, "treatment of an ocular diseases" refers to treating, preventing or inhibiting an ocular disease, such as macular degeneration, Wet AMD, Dry AMD, macular edema, DME, CME, ocular retinopathies, diabetic reinopathy, PDR, ischemic retinopathy, choroidal neovascularization, retinal neovascularization, RP, pathologic myopia, ocular histoplasmosis (OH), neovascular glaucoma, retinopathy of prematurity, the after effects of corneal transplantation and control of post-surgical ocular inflammation, e.g., after cataract surgery.

Additional indications include use in coronary disease, hypertension, renal disease, heart failure including congestive heart failure and diabetes.

What is claimed is:

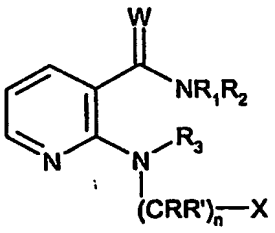
1. A method of preventing or treating diseases characterized by cell proliferation and inflammation, coronary disease, hypertension, renal diseases, diabetes and ocular diseases and conditions in a mammal, which comprises administering pharmaceutically effective amounts of a combination of:

(a) a VEGF inhibitor compound; and

(b) one or more second therapeutic agents selected from the group consisting of:

i. angiostatic steroids;
ii. photodynamic therapy;
iii. implants containing corticosteroids;
iv. AT1 receptor antagonists;
vi. ACE inhibitors;
vii. cyclooxygenase inhibitors;
viii. IGR-1R inhibitors;
ix. mTOR kinase inhibitors;
x. somatostatin receptor antagonists;
xi. PI3K inhibitors;
xii. Raf kinase inhibitors; and
xiii. PKC inhibitors.

2. A method according to Claim 1, wherein the VEGF inhibitor compound is of the formula (I)



(I)

wherein for formula (I) the variables are:

n is from 1 up to and including 6;

W is O or S;

R_1 and R_3 represent independently of each other hydrogen, lower alkyl or lower acyl;

R_2 represents an cycloalkyl group, an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

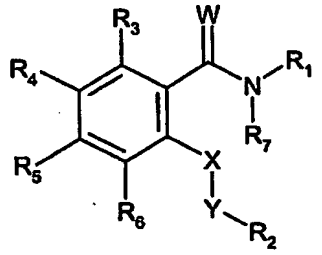
R and R' are independently of each other hydrogen or lower alkyl; and

X represents an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

or of a *N*-oxide or a possible tautomer thereof;

or of a pharmaceutically acceptable salt.

3. A method according to Claim 1, wherein the VEGF inhibitor compound is a compound of formula (II)



(II)

wherein the substituents for compounds of formula (II) are:

W is O or S;

X is NR_8;

Y is CR_9R_{10}-$(CH_2)_n$, wherein

R_9 and R_{10} are independently of each other hydrogen or lower alkyl; and

n is an integer of from and including 0 to and including 3; or

Y is SO_2;

R_1 is aryl;

R_2 is a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms with the exception that R_2 cannot represent 2-phthalimidyl, and in case of Y = SO_2 cannot represent 2,1,3-benzothiadiazol-4-yl;

any of R_3, R_4, R_5 and R_6, independently of the other, is H or a substituent other than hydrogen; and

R_7 and R_8, independently of each other, are H or lower alkyl;

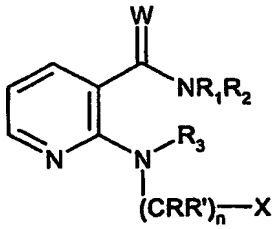
or a *N*-oxide or a pharmaceutically acceptable salt thereof.

4. A method of preventing or treating diseases characterized by cell proliferation and inflammation, coronary disease, hypertension, renal diseases, diabetes and ocular diseases and conditions in a mammal, which comprises administering pharmaceutically effective amounts of a combination of:

(a) a VEGF inhibitor compound; and

(b) one or more second therapeutic agents selected from the group consisting of VISUDYNE, PREXIGE, CELEBREX, VIOXX, RAD001, SOM230, octreotide, QAN697, anecortave, triamcinolone, fluocinolone, dexamethasone, DIOVAN and CIBACEN.

5. A method according to Claim 4, wherein the VEGF inhibitor compound is of the formula (I)



(I)

wherein for formula (I) the variables are:

n is from 1 up to and including 6;

W is O or S;

R_1 and R_3 represent independently of each other hydrogen, lower alkyl or lower acyl;

R_2 represents an cycloalkyl group, an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

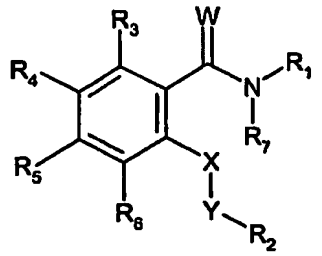
R and R' are independently of each other hydrogen or lower alkyl; and

X represents an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

or of a *N*-oxide or a possible tautomer thereof;

or of a pharmaceutically acceptable salt.

6. A method according to Claim 4, wherein the VEGF inhibitor compound is a compound of formula (II)



(II)

wherein the substituents for compounds of formula (II) are:

W is O or S;

X is NR_8;

Y is CR_9R_{10}-$(CH_2)_n$, wherein

R_9 and R_{10} are independently of each other hydrogen or lower alkyl; and

n is an integer of from and including 0 to and including 3; or

Y is SO_2;

R_1 is aryl;

R_2 is a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms with the exception that R_2 cannot represent 2-phthalimidyl, and in case of Y = SO_2 cannot represent 2,1,3-benzothiadiazol-4-yl;

any of R_3, R_4, R_5 and R_6, independently of the other, is H or a substituent other than hydrogen; and

R_7 and R_8, independently of each other, are H or lower alkyl;

or a *N*-oxide or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising:

(a) a VEGF inhibitor compound; and

(b) one or more second therapeutic agents selected from the group consisting of:

i. angiostatic steroids;

ii. photodynamic therapy;

iii. implants containing corticosteroids;

iv. AT1 receptor antagonists;

vi. ACE inhibitors;

vii. cyclooxygenase inhibitors;

viii. IGR-1R inhibitors;

ix. mTOR kinase inhibitors;

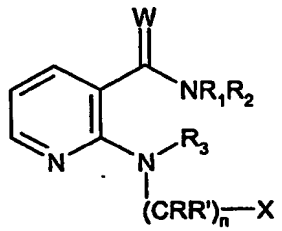
x. somatostatin receptor antagonists;

xi. PI3K inhibitors;

xii. Raf kinase inhibitors; and

xiii. PKC inhibitors.

8. A pharmaceutical composition according to Claim 7, wherein the VEGF inhibitor compound is of formula (I)



(I)

wherein for formula (I) the variables are:

n is from 1 up to and including 6;

W is O or S;

R_1 and R_3 represent independently of each other hydrogen, lower alkyl or lower acyl;

R_2 represents an cycloalkyl group, an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

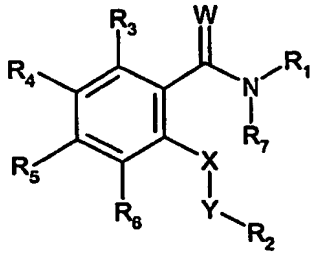
R and R' are independently of each other hydrogen or lower alkyl; and

X represents an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

or of a *N*-oxide or a possible tautomer thereof;

or of a pharmaceutically acceptable salt.

9. A pharmaceutical composition according to Claim 7, wherein the VEGF inhibitor compound is a compound of formula (II)



(II)

wherein the substituents for compounds of formula (II) are:

W is O or S;

X is NR_8;

Y is CR_9R_{10}-$(CH_2)_n$, wherein

R_9 and R_{10} are independently of each other hydrogen or lower alkyl; and

n is an integer of from and including 0 to and including 3; or

Y is SO_2;

R_1 is aryl;

R_2 is a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms with the exception that R_2 cannot represent 2-phthalimidyl, and in case of Y = SO_2 cannot represent 2,1,3-benzothiadiazol-4-yl;

any of R_3, R_4, R_5 and R_6, independently of the other, is H or a substituent other than hydrogen; and

R_7 and R_8, independently of each other, are H or lower alkyl;

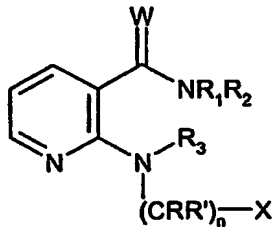
or a *N*-oxide or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising:

(a) a VEGF inhibitor compound; and

(b) one or more second therapeutic agents selected from the group consisting of VISUDYNE, PREXIGE, CELEBREX, VIOXX, RAD001, SOM230, octreotide, QAN697, anecortave, triamcinolone, fluocinolone, dexamethasone, DIOVAN and CIBACEN.

11. A pharmaceutical composition according to Claim 10, wherein the VEGF inhibitor compound is of the formula (I)



(I)

wherein for formula (I) the variables are:

n is from 1 up to and including 6;

W is O or S;

R_1 and R_3 represent independently of each other hydrogen, lower alkyl or lower acyl;

R_2 represents an cycloalkyl group, an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

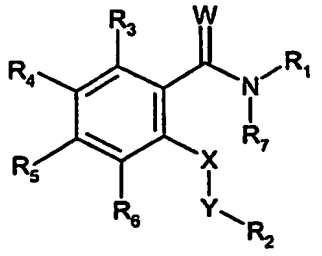
R and R' are independently of each other hydrogen or lower alkyl; and

X represents an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

or of a *N*-oxide or a possible tautomer thereof;

or of a pharmaceutically acceptable salt.

12. A pharmaceutical composition according to Claim 10, wherein the VEGF inhibitor compound is



(II)

wherein the substituents for compounds of formula (II) are:

W is O or S;

X is NR_8;

Y is CR_9R_{10}-$(CH_2)_n$, wherein

R_9 and R_{10} are independently of each other hydrogen or lower alkyl; and

n is an integer of from and including 0 to and including 3; or

Y is SO_2;

R_1 is aryl;

R_2 is a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms with the exception that R_2 cannot represent 2-phthalimidyl, and in case of Y = SO_2 cannot represent 2,1,3-benzothiadiazol-4-yl;

any of R_3, R_4, R_5 and R_6, independently of the other, is H or a substituent other than hydrogen; and

R_7 and R_8, independently of each other, are H or lower alkyl;

or a *N*-oxide or a pharmaceutically acceptable salt thereof.

13. A method of Claim 1, wherein the diseases that are triggered by persistent angiogenesis are selected from psoriasis, restenosis, e.g., stent-induced restenosis, endometriosis, Crohn's disease; arthritis, such as rheumatoid arthritis; hemangioma; angiofibroma; ocular diseases, such as Wet AMD, Dry AMD, macular edema, DME, CME, diabetic reinopathy, PDR, ischemic retinopathy, choroidal neovascularization, retinal neovascularization, RP and pathologic myopia; renal diseases, such as glomerulonephritis; diabetic nephropathy; malignant nephrosclerosis; thrombotic microangiopathic syndromes; transplant rejections and glomerulopathy; fibrotic diseases, such as cirrhosis of the liver; mesangial cell-proliferative diseases; arteriosclerosis; injuries of the nerve tissue and for inhibiting the re-occlusion of vessels after balloon catheter treatment, for use in vascular prosthetics or after inserting mechanical devices for holding vessels open, such as, e.g., stents, as immunosuppressants, as an aid in scar-free wound healing, and for treating age spots and contact dermatitis.

14. A method according to Claim 1, where the diseases characterized by cell proliferation and infiltration of inflammatory cells include inflammation, RHA, asthma, chronic bronchitis, artheroschlerosis and transplant rejection.

15. A method according to Claim 1, where the diseases are rheumatoid arthritis, ocular neovascularization, psoriasis, lymphangiogenesis, angiotension, hypertension, Wet AMD, DME, diabetic reinopathy, retinophathies, ocular neovascularization, coronary disease, hypertension, renal disease, heart failure including congestive and diabetes.

16. A method according to Claim 1, where said treatment of said ocular disease refers to treating, preventing or inhibiting of an ocular disease, selected from macular degeneration, Wet AMD, Dry AMD, macular edema, DME, CME, ocular retinopathies, diabetic reinopathy, PDR, ischemic retinopathy, choroidal neovascularization, retinal neovascularization, RP, pathologic myopia, OH, neovascular glaucoma, retinopathy of prematurity, the after effects of corneal transplantation and control of post-surgical ocular inflammation, e.g., after cataract surgery.

Abstract of the Disclosure

A method of preventing or treating diseases characterized by cell proliferation and inflammation, coronary disease, hypertension, renal diseases, diabetes and ocular diseases and conditions in a mammal, which comprises administering pharmaceutically effective amounts of a combination of:

(a) a VEGF inhibitor compound; and

(b) one or more second therapeutic agents selected from the group consisting of:

i. angiostatic steroids;
ii. photodynamic therapy;
iii. implants containing corticosteroids;
iv. AT1 receptor antagonists;
vi. ACE inhibitors;
vii. cyclooxygenase inhibitors;
viii. IGR-1R inhibitors;
ix. mTOR kinase inhibitors;
x. somatostatin receptor antagonists;
xi. PI3K inhibitors;
xii. Raf kinase inhibitors; and
xiii. PKC inhibitors.

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